REMARKS

Claims 1, 9, and 12 are amended herein, without prejudice to renewal of any removed subject matter. Claims 1 and 9 are amended to remove the term "commonly." Claim 12 is amended to refer solely to an inhibitor of a multi-drug resistance protein.

The specification is amended solely to insert the required sequence identifiers.

No new matter is added. Reconsideration of the subject application is respectfully requested.

Priority Claim

Applicants thank the Examiner for acknowledging the claim for foreign priority. Applicants request that the requirement for the submission of a certified copy of U.K. Application No. 9930519.5 be held in abeyance until the claims are in condition for allowance.

Sequence Listing

Pages 11, 13, 15 and 16 are amended herein to insert the required sequence identifiers, thereby overcoming the objection to the specification.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 9-13 and 16 were rejected under 35 U.S.C. § 112, first paragraph as allegedly the specification does not provide enablement for the *in vivo* use of the nucleic acids encoding the fusion protein. Applicants respectfully disagree with this assertion.

The Murphy citation quoted by the Examiner in connection with this merely suggests that there could be problems that are only associated with treating disorders of the cytoplasmic and plasma membrane. However, Applicants respectfully submit this is not of particular relevance to the current application. By contrast, there are reports in the scientific literature which demonstrate that *in vivo* injection of DNA encoding VP22 fusions does indeed have effect *in vivo* (e.g. see *Gene Therapy* 10(4):314-325, 2003; *Gastroenterology* 123(2):608-618, 2002, copies of which will be submitted upon the Examiner's request).

With respect to aggregated compositions (see the Office action, page 5), Applicants submit that the application fully enables production of such compositions and the precise nature of the oligonucleotide or polynucleotide is not critical (e.g. see guidance in the application at

page 7, paragraph 3 to page 8, paragraph 1, and also in the examples which describe making such compositions). Hence, Applicants respectfully submit that the claims are fully enabled.

Applicants thank the Examiner for noting that the specification is enabling for the *in vitro* use of conjugates including either the fusion protein of the disclosure or the nucleic acids encoding the fusion protein. Applicants also thank the Examiner for noting that the specification is enabling for the *in vivo* use of the fusion proteins of the disclosure.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 9-13 are 16 were rejected as allegedly being indefinite for the use of the terms "commonly," and the use of the term "Acf." Applicants respectfully disagree with these assertions. However, claims 1, 9 and 12 have been amended to remove these terms, thereby removing the rejection.

Rejections under 35 U.S.C. § 103

Claims 1-6 and 9-10 were rejected as allegedly being obviousness over O Hare et al., (WO 98/32866) and Dilber et al., and the application (at page 3, lines 14-28 and page 8, line 1-10). Claims 11-13 and 16 were also rejected as allegedly being obvious over O Hare et al., (WO 98/32866) and Dilber et al., and the disclosure of the present specification. Applicants respectfully disagree with this assertion.

Applicants respectfully submit that the present claims specify a new and particularly effective synergistic combination, not disclosed or suggested by O'Hare. Indeed, the Dilber et al. citation teaches away from the particular combination of the claims, as it uses a different combination, namely VP22 and a suicide protein. Thus Applicants submit that there is no incentive to modify the teachings of O'Hare et al. with the teachings of Dilber et al.

Furthermore, the legal standard applicable to determinations of obviousness based on a combination of references was reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 472-3, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would suggest to one of ordinary skill in the art that this process shall be carried out and would have a reasonable expectation of success viewed in the light of the prior art. Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure [emphasis added, citation omitted].

Thus, (1) the prior art must suggest, or provide an incentive for a combination of references, (2) the combination as suggested or motivated by the art must yield the process claimed, and (3) the prior art must provide an expectation of success. However, at no point must the applicants' disclosure be used to suggest, or provide incentive for, a combination of references. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

If any minor matters remain to be addressed before a Notice of Allowance is issued, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Marked-up Version of Amended Specification and Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

In the specification:

Please replace the paragraph found in the specification at page 11, lines 18-21 with the following paragraph:

--5'GATCCTATGGGGCAGGTGGGACGGCAGCTCGCCATCATCGGGGACGA CATCAACCGACGCTATCGG (SEQ ID NO: 1)

5'GATCCCGATAGCGTCGGTTGATGTCGTCCCCGATGATGGCGAGCTGCCGTC CCACCTGCCCCATG (SEQ ID NO: 2)--

Please replace the paragraph found in the specification at page 13, lines 25-26 with the following paragraph:

--5' CCC CCA CCA CTT CCC CTC TC 3' (SEQ ID NO: 3), and labeled at the 5' end with FITC.--

Please replace the paragraph found in the specification at page 15, line 14 with the following paragraph:

--5' CCC CCA CCA CTT CCC CTC TC 3' (SEQ ID NO: 4)--

Please replace the paragraph found in the specification at page 16, line 8, with the following paragraph:

--5' GUUUUCCCUGAU GAGGCCGAAAGGCCGAAAUUCUCC 3' (SEQ ID NO: 5),--

In the claims:

1. (Amended) A method of reducing proliferation of cells comprising: (a) exposing said cells to a composition comprising at least one polypeptide comprising an amino acid sequence with the transport function of herpesviral VP22 protein, said polypeptide being coupled to al least one functionally active amino acid sequence, wherein the functionally active amino acid sequence is a protein or peptide which can regulate cell cycle progression, or functional analogue thereof; or exposing said cells to a composition comprising nucleic acids encoding said protein or peptide and (b) exposing said cells to at least one agent to further stimulate cells death, said agent selected from: drugs which can induce cell cycle arrest, cytotoxic chemotherapeutic drugs [commonly] used as part of a treatment programme of malignant disease, DNA damaging agents, agents which increase cellular sensitivity to DNA damage, and cytotoxic amounts of radiation.

2. (Reiterated) A method according to claim 1, wherein said cells are hyperproliferating cells.

3. (Reiterated) A method according to claim 1, wherein said coupled polypeptide can induce apoptosis, or can arrest cells from the cell cycle.

4. (Reiterated) A method according to claim 1, wherein said VP22 coupled polypeptides are aggregated compositions of VP22 non-covalently associated with oligonucleotides or polynucleotides.

5. (Reiterated) A method according to claim 2, wherein said cells are cancer cells.

6. (Reiterated) A method according to claim 3, wherein said polypeptide is a cyclin-dependent kinase inhibitor.

7. (Reiterated) A composition comprising

(a) a coupling product between a protein with the transport function of VP22 and a protein which can regulate cell cycle progression; and

(b) at least one agent to further stimulate cell death, said agent being selected from the group consisting of drugs which can induce cell cycle arrest, cytotoxic chemotherapeutic drugs commonly used as part of a treatment of malignant disease, DNA damaging agents, and agents which increase cellular sensitivity to DNA damage;

in combination with a suitable pharmaceutical excipient.

8. (Reiterated) A method of manufacture of a medicament to reduce cell proliferation comprising formulating a preparation comprising (a) a coupling product between a protein with the transport function or VP22 and a protein which can regulate cell cycle progression, and (b) at least one agent to further stimulate cell death, said agent being selected from the group consisting of drugs which can induce cell cycle arrest, cytotoxic chemotherapeutic drugs commonly used as part of a treatment of malignant disease, DNA damaging agents, and agents which increase cellular sensitivity to DNA damage, with a suitable pharmaceutical excipient.

9. (Amended) A method of reducing proliferation of cells comprising: (a) a coupling product between a protein with the transport function of VP22and a protein which can regulate cell cycle progression, and (b) at least one agent to further stimulate cells death, said agent being selected from the group consisting of: drugs which can induce cell cycle arrest, cytotoxic chemotherapeutic drugs [commonly] used as part of a treatment programme of malignant disease, DNA damaging agents, and agents which increase cellular sensitivity to DNA damage, in combination with a suitable pharmaceutical excipient, thereby reducing proliferation of said cells.

10. (Reiterated) A method according to claim 1, wherein the polypeptide is coupled to a plurality of functionally active amino acid sequences.

11. (Reiterated) A method according to claim 1, comprising further (c) exposing said cells to at least one agent that can prevent export from the cell of any one of the agents administered in a) and/or b), wherein said exposure occurs after step a) and/or step b).

12. (Amended) A method according to claim 11, wherein said agent that can prevent export from the cell of any one of the agents administered in a) and/or b) is [an Acf protein or] an inhibitor of the multi-drug resistance protein.

13. (Reiterated) A method according to claim 12, wherein said agent is an antisense molecule.

14. (Reiterated) The composition of claim 7, further comprising (c) at least one agent that can prevent export from the cell of any one of the agents (a) and/or (b).

15. (Reiterated) The method of claim 8, wherein the preparation further comprises (c) at least one agent that can prevent export from the cell of any one of the agents (a) and/or (b).

16. (Reiterated) The method of claim 9, and wherein said preparation further comprises (c) at least one agent that can prevent export from the cell of any one of the agents (a) and/or (b).